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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	**PAPER NUMBER**
1631	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/549,246	SCHROEDER ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/13/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicant's amendments and request for reconsideration in the communication filed on 13 April 2010 are acknowledged and the amendments are entered.

Claims 1-22 and 24-34 are pending in the instant application.

Claims 1-22 and 24-34 are examined in the instant Office action.

Information Disclosure Statement

The information disclosure statement filed on 13 April 2010 has been considered.

Oath/Declaration

The following objection to the declaration is reiterated:

The declaration filed on 7 June 2006 is defective because all of the copies of the declaration do not list each inventor. In this instance, each copy of the declaration only includes a single inventor. See MPEP 201.03 II B and MPEP 605.04(a) for rules governing the signatures and listing of inventors on oaths and declarations submitted for an invention.

Response to Arguments:

Applicant requested that this objection be held in abeyance, and potentially be corrected at a later date.

Withdrawn Objections/Rejections

The objection to he abstract of the disclosure because the "sentence" is a fragment and not a full sentence (i.e. it lacks a verb) is withdrawn in view of amendments filed to the specification on 13 April 2010.

The objection to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of amendments filed to the specification on 13 April 2010.

The objection to claim 1 because of informalities is withdrawn in view of amendments filed to the instant claim on 13 April 2010.

The rejections of claims 2, 4-5, 8, and 16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of amendments filed to the instant set of claims on 13 April 2010.

The rejections of claims 1-25 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter are withdrawn in view of amendments filed to the instant set of claims on 13 April 2010.

ALL of the prior art rejections under 35 U.S.C. 102 and 35 U.S.C. 103 are withdrawn in view of amendments filed to the instant set of claims on 13 April 2010.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #1:

Claims 1, 3, 6, 9, 12, 21-22, 24, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. [Journal of the American Chemical Society, 1999, volume 121, pages 10671-10679] in view of Negin et al. [Journal of the American Chemical Society, 2002, volume 124, pages 2911-2916] as evidenced by the definition of Denaturation [Dorland's Illustrated Medical Dictionary, 2007].

Discussion of Independent Claims 1 and 30:

Claim 1 is drawn to a method for determining the extent of degradation expressed in terms of a quality value. The method comprises separating the biomolecule sample by one or more molecular characteristics, using a device, to generate measured data. The method comprises extracting feature(s) from the data by data analysis and determining a quality value (which indicated the extent of degradation of the biomolecule sample) from the features using a quality algorithm. This quality algorithm involves collecting a statistically significant number of trial measured data covering a prescribed set of biomolecule samples and assigning a quality label (which indicates the extent that the trial measured data exhibits signs of degradation) to each trial measured data, extracting features from the trial measured data using analysis. The quality algorithm also comprises determining functional interrelations among the quality labels and one or more of the extracted features. The quality algorithm also comprises assigning a rating factor to every functional interrelation and specifying the functional interrelation that has the highest rating factor as the quality algorithm.

Claim 30 is drawn to similar subject matter of determining the extent of biomolecule degradation as in claim 1, except claim 30 is broader than claim 1 by only requiring separation the biomolecule sample to generate data, extracting features from this data, and determining quality values indicating the extent of degradation of the biomolecule sample.

The article of Carbeck et al. studies protein charge ladders derived using capillary electrophoresis on a Beckman P/ACE 5500 [title and final paragraph before

"Acknowledgement" on page 10679 of Carbeck et al.]. Specifically, electropherograms of protein mixtures are taken (such as in Figure 1A on page 10672 of Carbeck et al.) wherein the mixture is of the same generic protein molecule with varying numbers of amines acetylated. Since there is an integer distribution of the number of acetylated amines, the electropherogram of the mixture (i.e. Figure 1A of Carbeck et al.) resembles a ladder wherein each "rung" represents a version of the modified protein with a specific and different number of amines acetylated. In other words, the mixture of differently acetylated proteins is separated such that each "rung" represents a version of the protein with the same number of amines acetylated. It is noted that when an amine is acetylated, the resulting acetylated amine- unlike the normal amine- is incapable of attaining a positive charge. It is this difference in electrostatic change between the "rungs" which allows the capillary electrophoresis to separate the rungs of the ladder [page 10673 of Carbeck et al.]. Consequently, the integer distribution of the number of acetylated amines in Figure 1A of Carbeck et al. is also a discrete distribution of charge on the partially amine acetylated protein mixture.

Therefore, Figure 1 of Carbeck et al. extracts a statistically significant number of trial measured data (i.e. the migration time for each rung of the ladder) which is converted according to equation 6 on page 10673 of Carbeck et al. to electrophoretic mobilities (i.e. the ordinate axis in Figure 1B of Carbeck et al.) A quality label is then assigned to each point of measured data using the abscissa of Figure 1B of Carbeck et al. (i.e. a value of $n\Delta Z_{seq}$ which represents the product of the number of acetylations of particular rung and the expected change in charge of the protein resulting from each

amine being acetylated- under the pH and buffer conditions of Carbeck et al., this value is -1). It is noted that the term “quality” is exemplified, but not defined, in the instant disclosure. In the absence of such a definition, the term quality is interpreted broadly to encompass the quality of electrostatic properties, such as $n\Delta Z_{seq}$.

The plots of Figure 1 of Carbeck et al. are used to determine the features of charge of the protein in the absence of acetylations (i.e. in Figure 1B of Carbeck et al., the x-intercept of the line tangent to the charge ladder data point "curve" at the curve’s y-intercept), and the mass and/or size of the protein (inversely proportional to the slope of the above tangent line). Equations 7-9 on page 10673 of Carbeck et al. and equation 15 on page 10675 of Carbeck et al. list the functional interrelations between the quality labels and features (i.e. the electrophoretic mobilities, charge, mass, and radius) of the protein. Specifically, equation 15 on page 10675 of Carbeck et al. uses Debye-Huckel theory to determine the radius of the protein from electrostatic properties. When this functional interrelation is applied to the charge ladder data in Figure 3 of Carbeck et al., the best quality of agreement (i.e. rating or quality value) occurs when the radius of the protein is set to 2.1 nm [see Figure 3 of Carbeck et al. and the paragraph of text bridging pages 10675-10676 of Carbeck et al.].

The article of Carbeck et al. does not use protein charge ladders to determine the extent of degradation of a protein.

The article of Negin et al. associates changes in measurements of electrostatic interactions with the folding of a protein by use of protein charge ladders [title]. Specifically, charge ladders as a function of temperature are used to assess the thermal

denaturation of lysozyme and cytochrome c [last sentence of the full paragraph of column 1 on page 2912 of Negin et al.]. When a protein denatured, the protein is interpreted to be degraded in that the protein loses its ability to perform biological activity [Definition of Denaturation]. Attention is drawn to Figures 3-4 on page 2913 of Negin et al. Specifically, Figure 3 of Negin et al. performs the analysis of Figure 1B of Carbeck et al. twice (once at 25C when the proteins are folded and once at 75C when the proteins are denatured). From the changes in slopes between the two fitted lines, the radius of the protein increases from the folded size of 20.1A to a denatured size of 22.3A. When similar analyses are undertaken at various values of temperature and the sizes of the protein is plotted, Figure 4 of Negin et al. indicates a sigmoidal transition from the fully folded states to a denatured globule. Consequently, using the study of Negin et al., the measured quality value of size (or radius) of the protein reflects the degree of degradation (i.e. denaturation) of the protein.

With regard to claim 3, Figure 3 of Carbeck et al. illustrates functions that are adaptively fit to the data by adapting or varying the value of the radius.

With regard to claim 6, the discrete classes of Figure 1 of Carbeck et al. are the discrete rungs of the charge ladder wherein each discrete class is assigned a quality label in Figure 1B.

With regard to claim 9, the charge ladder in Figure 1A is subdivided into segments based on the number of acetylated amines (i.e. the first rung has no acetylated amines, the second rung has one acetylated amine, and so on...)

With regard to claim 12, Figure 1B of Carbeck et al. illustrates fitting data to a curve based on the slope and y-intercept of the interpolating straight line fitted to the points falling within the bounds of the segment.

With regard to claims 21-22, the charge ladder in Figure 1 of Carbeck is of the protein bovine carbonic anhydrase II.

With regard to claim 24, Figure 1A of Carbeck et al. is an electropherogram.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quality/radius/charge determination method of Carbeck et al. by applying the technique to measure thermal degradations of proteins as in Negin et al. wherein the motivation would have been that this method of determining protein denaturation/degradation using protein change ladders is simple, generally applicable to any protein capable of producing a charge ladder, and only relies on straightforward protein modifications (i.e. no genetic manipulations are required) [last full paragraph on column 2 on page 2915 of Negin et al. and Conclusion of Negin et al. on page 2915-2916].

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al. This argument is not persuasive because the combination of the Carbeck et al. and Negin et al. teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #2:

Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation as applied to claims 1, 3, 6, 9, 12, 21-22, 24, and 30 above, and further in view of Allison et al. [Biophysical Journal, volume 68, 1995, pages 2261-2270] in view of Allison et al. [Macromolecules, 1992, volume 25, pages 3971-3978]. This second reference of Allison et al. is referred to as Allison et al. (1992) throughout this Office action.

Claim 25 is drawn to similar subject matter as claim 1, except as a software program or product.

Claim 26 is drawn to similar subject matter as claim 1, except as an apparatus.

Carbeck et al. and Negin et al. make obvious a method for assessing biomolecular degradation by determining quality value of the biomolecule sample, as discussed above.

Carbeck et al. and Negin et al. do not teach software or computing apparatus for executing this method.

Allison et al. teaches the computational modeling of electrostatics of a protein (i.e. lysozyme). Specifically, Figures 4-6 on page 2267 of Allison et al. illustrate several modeling algorithms for determining the charge on lysozyme as a function of pH (wherein computationally changing pH is the computational equivalent of modifying degree of acetylation as it also computationally alters charge on the protein). However, Allison et al. does not teach software of a physical structural apparatus.

The article of Allison et al. (1992) does use computer and software for calculating electrostatics around a sphere. Specifically, the second full paragraph on column 1 on page 3977 of Allison et al. (1992) teaches use of a Silicon Graphics 4D/380 computer and its CPU.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quality determination method of Carbeck et al. and the degradation assessment method of Negin et al. by use of the computers in Allison et al. (1992) wherein the motivation would have been that the computers of Allison et al. (1992) expedite the processing of data (see the second full paragraph on column 1 on page 3977 of Allison et al. (1992)). There would have been a reasonable expectation of success in applying the computational apparatus of Allison et al. (1992) to the

empirically derived charge ladders of Carbeck et al. because the article of Allison et al. demonstrates that charge ladders (and charge ladder-like modeling) are derivable both computationally and empirically.

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al., Allison et al. or Allison et al. (1992). This argument is not persuasive because the combination of the Carbeck et al., Negin et al., Allison et al. and Allison et al. (1992) teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #3:

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation as applied to claims 1, 3, 6, 9, 12, 21-22, 24, and 30 above, and further in view of Greiner et al. [Bioforum, volume 23, 2000, pages 751-754; German article].

Claim 7 is further limiting wherein seven classes are established for the quality label.

Carbeck et al. and Negin et al. make obvious a method for assessing biomolecular degradation by determining quality value of the biomolecule sample, as discussed above.

Carbeck et al. and Negin et al. do not teach a quality label with seven classes.

Greiner et al. studies analysis of biomolecules by lab-on-a-chip technologies.

Specifically, Figure 4 on page 754 of Greiner et al. teaches a protein ladder with seven rungs (i.e. there are actually nine "rungs," but two act as markers).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quality determination method of Carbeck et al. and the degradation assessment method of Negin et al. by use of the seven rung ladder of Greiner et al. because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, the seven rung ladder is an alternate ladder obtained from electrophoresis than the ladder obtained in Carbeck et al. There would have been a reasonable expectation of success in combining Carbeck et al. and Greiner al. because they pertain to the analogous field of protein ladders.

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al. or Greiner et al. This argument is not persuasive because the combination of the Carbeck et al.,

Negin et al., and Greiner et al. teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #4:

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation as applied to claims 1, 3, 6, 9, 12, 21-22, 24, and 30 above, and further in view of Foley [Analytical Chemistry, 1987, volume 59, pages 1984-1987].

Claim 11 is further limiting wherein the geometry of each peak is quantitatively determined.

Carbeck et al. and Negin et al. make obvious a method for assessing biomolecular degradation by determining quality value of the biomolecule sample, as discussed above.

Carbeck et al. and Negin et al. do not teach quantitative determination of peak geometry.

Foley studies quantitative analysis of peak shape and geometry [see title and abstract].

Specifically, Figure 1 on page 1985 of Foley teaches peak geometry analysis.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quality determination method of Carbeck et al. and the degradation assessment method of Negin et al. by use of the peak geometrical

analysis of Foley wherein the motivation would have been that quantitative peak shape analysis yields important statistical values in a variety of biological fields (including analytical chemistry which is the field of technology of the protein charge ladders) [see first paragraph of the introduction of Foley].

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al. or Foley. This argument is not persuasive because the combination of the Carbeck et al., Negin et al., and Foley teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #5:

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation in view of Allison et al. in view of Allison et al. (1992) as applied to claims 1, 3, 6, 9, 12, 21-22, 24-26, and 30 above, and further in view of Walther [Mathematical Methods in the Applied Sciences, 1999, volume 22, pages 301-316].

Claim 13 is further limiting comprising using the rolling ball algorithm.

Carbeck et al., Negin et al., Allison et al., and Allison et al. (1992) make obvious a computational method for determining quality values and extents of degradations of biomolecule samples, as discussed above.

Carbeck et al., Negin et al., Allison et al., and Allison et al. (1992) do not teach use of the rolling ball algorithm to smooth curves.

The article of Walther teaches a generalization of a rolling theorem for the smoothing of surfaces (see title and abstract).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the empirical quality determination method of Carbeck et al., the degradation analysis of Negin et al., the computational modeling of Allison et al., and the computational tools of Allison et al. (1992) by use of the rolling ball method of Walther wherein the motivation would have been that smoothing computational generated data makes the electrostatic data of Carbeck et al., Negin et al., Allison et al., and Allison et al. (1992) more amenable to in depth mathematical analysis [see abstract and introduction of Walther].

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al., Allison et al., Allison et al. (1992), or Walther. This argument is not persuasive because the

combination of the Carbeck et al., Negin et al., Allison et al. Allison et al. (1992), and Walther teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #6:

Claims 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation in view of Allison et al. in view of Allison et al. (1992) as applied to claims 1, 3, 6, 9, 12, 21-22, 24-26, and 30 above, and further in view of Bruneau [J. Chem. Inf. Comput. Sci., 2001, volume 41, pages 1605-1616].

Claim 17 is further limiting wherein a neural network is employed.

Claim 18 is further limiting wherein the neural network encompassed a Bayesian method.

Claim 19 is further limiting wherein the complexity of the functional interrelations is obtainable by iterative additions of hidden neurons to the neuronal network.

Carbeck et al., Negin et al., Allison et al., and Allison et al. (1992) make obvious a computational method for determining quality value and assessing degradation of a biomolecule sample, as discussed above.

Carbeck et al., Negin et al., Allison et al., and Allison et al. (1992) do not teach use of neural networks.

The article of Bruneau teaches a search for predictive generic model of aqueous solubility of proteins using Bayesian neural nets [see title and abstract]. This

determination of solubility involves calculations of electrostatic properties on the surface of the protein [see Table 2 of Bruneau on page 1608]. The complexity of the interrelations is obtained by iterative additions of hidden nodes in the neural network [see Scheme 1 and last full paragraph on page 1609 of Bruneau].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the empirical quality determination method of Carbeck et al., the degradation analysis of Negin et al., the computational modeling of Allison et al., and the computational tools of Allison et al. (1992) by use of the Bayesian neural networks of Bruneau wherein the motivation would have been that these advanced statistical techniques are a comprehensive approach for calculating a wider variety of descriptors in the most attractive and relevant model [see first paragraph in column 1 on page 1606 of Bruneau].

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al., Allison et al., Allison et al. (1992), or Bruneau. This argument is not persuasive because the combination of the Carbeck et al., Negin et al., Allison et al. Allison et al. (1992), and Bruneau teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #7:

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation in view of Allison et al. in view of Allison et al. (1992) in view of Bruneau as applied to claims 1, 3, 6, 9, 12, 17-19, 21-22, 24-26, and 30 above, and further in view of Schmidler et al. [Journal of Computational Biology, volume 7, 2000, pages 233-248].

Claim 20 is further limiting wherein the a-posteriori probability of the neuronal network is computed using a Bayesian method.

Carbeck et al., Negin et al., Allison et al., Allison et al. (1992), and Bruneau make obvious a computational method for determining degradation and quality values of the biomolecule sample using neural networks and Bayesian methods, as discussed above.

Carbeck et al., Negin et al., Allison et al., Allison et al. (1992), and Bruneau do not teach use of a-posteriori probability analysis.

The article of Schmidler et al. teaches Bayesian segmentation of the protein secondary structure. Specifically, the abstract teaches that posterior probabilities are determined.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the empirical quality determination method of Carbeck et al., the degradation analysis of Negin et al., the computational modeling of Allison et al., the computational tools of Allison et al. (1992) and the Bayesian neural networks of Bruneau by use of the a-posteriori probabilities of Schmidler et al. wherein it is obvious

to combine known elements in the prior art to yield a predictable result. In this instance using posterior probabilities is an alternate means of conducting the Bayesian analysis than in the prior art of Bruneau (which does not state whether posterior probability analysis was used). There would have been a reasonable expectation of success in combining Carbeck et al., Negin et al., Allison et al., Allison et al. (1992), Bruneau, and Schmidler et al. because all of the studies pertain to statistical analysis of protein electrostatics.

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al., Allison et al., Allison et al. (1992), Bruneau, or Schmidler et al. This argument is not persuasive because the combination of the Carbeck et al., Negin et al., Allison et al. Allison et al. (1992), Bruneau, and Schmidler et al. teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #8:

Claims 21-22, 27-28, and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation

as applied to claims 1, 3, 6, 9, 12, 21-22, 24, and 30 above, and further in view of Goldsborough [WO 00/66605; published 9 November 2000] in view of Pan et al. [Journal of Molecular Biology, 1997, volume 273, pages 7-13].

Claims 21-22 are further limiting wherein the biomolecules comprise RNA.

Independent claim 27 is drawn to similar subject matter as claim 1, except claim 27 only applies to RNA.

Independent claim 28 is drawn to similar subject matter as claim 30, except claim 27 only applies to RNA.

Claim 31 is further limiting from claim 30 wherein the biomolecule sample is RNA and the data is in the form of an electropherogram. Claim 32 is further limiting wherein this electropherogram is divided into segments.

Carbeck et al. and Negin et al. make obvious a method for assessing biomolecular degradation by determining quality value of the biomolecule sample, as discussed above. Figure 1 of Carbeck et al. teaches use of partitioned charge ladders displayed in the form of electropherograms.

Carbeck et al. and Negin et al. do not teach use of RNA as the biomolecular sample which degrades.

Goldsborough studies various modifications that could be made to nucleotides.

Specifically, Figure 5a of Goldsborough illustrates the schematic for acylation of RNA.

Furthermore, the article of Pan et al. studies the folding of RNA [title]. Specifically, Figure 4 on page 12 of Pan et al. demonstrates that RNA has a unfolding

and folding mechanism analogous to the proteins of Carbeck et al. and Negin et al. Also, Figure 3 on page 11 of Pan et al. has experimental data showing chemical denaturation of RNA.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quality determination method for proteins of Carbeck et al. and the protein degradation study of Negin et al. by use of the acylated RNA of Goldsborough because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, the acylation of RNA (instead of proteins) is an alternate means for synthesizing the same charge ladder using a different species of biomolecule. There would have been a reasonable expectation of success in combining Carbeck et al. and Goldsborough because each study successfully acylates biomolecules (i.e. Goldsborough shows a successful chemical mechanism for acylating RNA) which is the key requirement for generating charge ladders that result when each biomolecule undergoes electrophoresis. Additionally, there would have been a further expectation of success because, as shown above, both the RNA of Pan et al. and the proteins of Carbeck et al. and Negin et al. analogously fold or unfold depending the degree of the denaturing conditions of the buffer solution.

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al. or Goldsborough. This argument is not persuasive because the combination of the Carbeck et al., Negin et al., Goldsborough, and Pan et al. teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #9:

Claims 10, 14, 29, and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation in view of Goldsborough in view of Pan et al. as applied to claims 1, 3, 6, 9, 12, 21-22, 24, 27-28, and 30-32 above, and further in view of Strumberg et al. [Molecular and Cellular Biology, 2000, volume 20, pages 3977-3987].

Claim 10 is further limiting wherein an RNA sample is used involving all eight segments of the RNA.

Claim 14 is further limiting wherein the ratio of areas of the 18S fragment to the 28S fragment is determined.

Independent claim 29 is dependent claim 10 is independent form.

Claim 33 is dependent claim 31 with the additional limitations of a fast region, an 18S-region and a 28S region.

Claim 34 is drawn to similar subject matter as claim 12, except claim 34 is dependent from claim 33 rather than claim 9.

Carbeck et al., Negin et al., Goldsborough, and Pan et al. make obvious a method for assessing the degradation and determining quality value of an RNA, as discussed above. Figure 1B of Carbeck et al. illustrates fitting data to a curve based on the slope and y-intercept of the interpolating straight line fitted to the points falling within the bounds of the segment.

Carbeck et al., Negin et al., Goldsborough, and Pan et al. do not teach area ratios and specific regions of the RNA recited above.

The article of Strumberg et al. analyzes the structure of certain ribosomal RNA molecules [see introduction of Strumberg et al.] Specifically, Strumberg et al. shows the ratios of the areas of the 18S to the 28S fragment in Figure 1 on page 3978. Additionally, Figure 1 of Strumberg et al. illustrates a schematic of the entire RNA and therefore is interpreted to possess all eight segments recited in instant claim 14.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the RNA quality determination and degradation assessment methods of Carbeck et al., Negin et al., Goldsborough, and Pan et al. by use of the segments of RNA illustrated in Strumberg et al. because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, the eight segments of RNA in Strumberg et al. is an alternate means of observing the RNA than the charge ladders of Carbeck et al. and Negin et al. applied to the RNA of Goldsborough. There would have been a reasonable expectation of success in combining Strumberg et al. with the electrostatics and charge ladders of Carbeck et al. and Negin et al., the application of acylations to RNA taught in Goldsborough, and the

RNA folding study of Pan et al. because all of the studies pertain to electrophoresis of segmented portions of a biomolecule; in Strumberg et al., the observation of the RNA is slightly different that that of Carbeck et al. and Goldsborough (i.e. instead of an electrostatic ladder, the ladder in Strumberg et al. is based on geometric and sequence regions of the RNA).

More importantly, this combination of references has a reasonable expectation of success because there is no limitation in the instantly rejected claims requiring that these eight sections of RNA need to be involved in quality value analysis. In other words, while the instantly rejected claims only require that the portions of the RNA to POSSESS these regions of interest, the instant set of rejected claims AT MOST only require partitioning/dividing the electropherogram according to these regions, and DO NOT require any of these eight regions to be associated with the determination of a quality value associated with extent of degradation of the RNA.

Response to Arguments:

Applicant's arguments filed 13 April 2010 have been fully considered but they are not persuasive.

Applicant argues that the amendments to the instant claims reciting assessment of the extent of degradation of the sample are not taught in Carbeck et al., Goldsborough, or Strumberg et al. This argument is not persuasive because the combination of the Carbeck et al., Negin et al., Goldsborough, Pan et al., and Strumberg et al. teaches all of the limitations of the instantly rejected claims.

The following rejections are necessitated by amendment:

35 U.S.C. 103 Rejection #10:

Claims 2, 4-5, 8, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carbeck et al. in view of Negin et al. as evidenced by Denaturation as applied to claims 1, 3, 6, 9, 12, 21-22, 24, and 30 above, and further in view of Taylor et al. [Electrophoresis, volume 13, 1992, pages 162-168].

Claim 2 is further limiting comprising specifying one or more anomalous cases from among a prescribed number of potentially anomalous cases, extracting a number of prescribed features from the measured data of the biomolecule sample using data analysis for every anomalous case, analyzing the measured data using an associated anomalous-case algorithm in order to validate every anomalous case identified, and determining the magnitude of the anomaly involved from a combination of the anomalous cases present in order to determine the degree to which the biomolecule sample is anomalous.

Dependent claim 4 is drawn to similar subject matter as independent claim 1, except the method is conducted in a manner that detects anomalous cases. Claim 5 is further limiting wherein the functional interrelations among the anomalous-case labels and the various combinations of extracted features are determined using an adaptive approach. Claim 8 is further limiting wherein binary variables are used to recognize anomalous cases.

Claim 15 is further limiting wherein the extracted features are consecutively arranged in a list such that the information on the quality label and/or the anomalous case label will be progressively maximized as each additional feature is added, where each addition of a feature to the list defines a new combination of features. Claim 16 is further limiting wherein the arrangement of extracted features in the list is based on mutual information.

Carbeck et al. and Negin et al. make obvious a method for assessing biomolecular degradation by determining quality value of the biomolecule sample, as discussed above. Figure 1A of Carbeck et al. effectively specifies, determines the magnitudes, and labels the "anomalous cases" in the electropherogram; each artifact in Figure 1A of Carbeck et al. is binary in that the artifact is assigned a value of unity (an asterisk) is it exists, and zero (i.e. no asterisk) in the absence of an artifact. Furthermore, with regard to claims 15-16, Figure 1 and its caption in Carbeck et al. teach that the line is fit to the first five points (or rungs) of the charge ladder. In other words, as each feature is added (up to a consecutive value of five) the quality label is maximized by adding points to which the line is fit. This list of five rungs is based on mutual information from the electropherogram.

Consequently, while Carbeck et al. and Negin et al. teach identifying anomalous cases (in this case peak artifacts in electropherograms), Carbeck et al. and Negin et al. do not teach algorithms for extracting, differentiating, and validating anomalous cases from the relevant data.

The article of Taylor et al. studies use of principle component analysis to analyze two dimensional protein electropherograms [title]. Specifically, the abstract of Taylor et al. explains that multivariate principal component analysis is used to recognize, differentiate and validate outliers (i.e. anomalies) from relevant data.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the quality determination method of Carbeck et al. and the degradation assessment method of Negin et al. by use of principal component analysis to separate of anomalous (i.e. outlying) data from relevant data as in Taylor et al. wherein the motivation would have been that not only recognizing (and excluding) outliers increases the accuracy of the data, but also that the multivariate statistical approach is robust in that it can be applied generically to many proteins [first full paragraph in column 1 on page 163 of Taylor et al.].

Response to Arguments:

Applicant's arguments with respect to the instantly rejected claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Russell S. Negin/
Examiner, Art Unit 1631
5 July 2010